encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness." One skilled in the art must be motivated to select the claimed subgenus from the disclosed prior art genus. *See* M.P.E.P. § 2144.08, 2100-156 (Rev. 6, Sept 2007). In the present case no such motivation exists.

As noted by the Examiner, differences between the claimed compounds and those of the present invention include substitution of a trifluoromethyl group at the 4-position of the N-CH_2-phenyl group of Formula II. Ford-Hutchinson discloses no specific compounds having CF_3 at the corresponding position, but generically encompasses such substitution in a very broad genus. CF_3 is listed among 22 groups for the variable M, which is linked to an alkyl chain of zero to three carbon atoms, which is among a list of four other groups for any of R^1, R^2, R^3, R^4, R^5 and R^6. Thus, one skilled in the art beginning with the genus described in Ford-Hutchinson would need to decide to choose R^5 or R^6 to be other than hydrogen, choose $-(CH2)_nM$ rather than alkyl or alkenyl, select n to be zero, select CF_3 out of the 21 other possibilities and substitute this group at the 4-position of the phenyl to arrive at the present invention, with no teaching or indication that such group is preferred. Even in the "most preferred" embodiment (see page 7, line 34), CF_3 is listed among 14 choices for M, which is among three choices for any of R^1 to R^6. Applicants submit the Examiner is engaging in impressible hindsight with knowledge of the present invention to select CF_3 out of the many other possibilities.

Moreover, none of the specific compounds taught in Ford-Hutchinson have a CF_3 group at the 4-position of the N-CH_2-phenyl, thus teaching away from the claimed invention. The Examiner specifically refers to Example 24 taught in Ford-Hutchinson and alleges that one skilled in the art would be motivated by the teachings of Patani to modify this compound by substituting CF_3 for Cl. Applicants disagree. As the Examiner notes, Patani teaches that substitution of CF_3 or CN for Cl on a benzodiazepine derivative results in retention of CCK-A receptor activity. However, on the same page Patani teaches that substitution of CF_3 for Cl on a 5-benzyluracil derivative resulted in **less potent** uridine phosphorylase inhibition. Thus, Patani demonstrates that such substitution behaves differently depending on the specific chemical compound and target. Consequently, one skilled in the art would not be motivated to look for and take the teachings of totally unrelated structures and targets taught by Patanti and apply those

teachings to structure-activity relationships of tetrahydrocarbozole derivatives for either limiting cyclosporine induced nephrotoxicity or modulating the action of gamma secretase. Thus, in no way would Patani provide the necessary motivation to modify the examples taught in Ford-Hutchinson to arrive at the compounds presently claimed.

Furthermore, Claim 7 teaches compounds wherein R^{3a} is a hydrocarbon of 2 to 10 carbon atoms. Thus, one skilled in the art starting with Ford-Hutchinson would have to choose to modify the examples therein by substituting a CF_3 group at the 4-position of the N-CH_2-phenyl **and** substitute a hydrocarbon of 2 to 10 carbon atoms on the benzylic carbon. One skilled in the art would in no way be motivated to make both modifications.

With respect to Watanbe, Applicants submit the instant claims are non-obvious in view thereof. The instant claims require a $C(R^2)_2CO_2H$ group at a fixed position on the cyclohexene ring adjacent to the indole nitrogen. The nearest Watanbe comes to this is an amide or hydrazide group, attached directly to the ring (no -$C(R^2)$- spacer) at the opposite end, i.e., pointing in entirely the wrong direction. Watanbe also does not specifically teach CF_3 substitution on the phenyl ring or alkyl substitution on the benzylic carbon.

The Examiner argues that one skilled in the art would be motivated to try out the range of substituents taught by Ford-Hutchinson to arrive at the instantly claimed compounds and that Watanbe would provide the additional motivation to make pharmaceutical compositions and use them for treating Alzheimer's disease. First, obvious to try is not the proper standard to conduct an obviousness determination. To establish a *prima facie* of obviousness, one skilled in the art must be motivated to select the sub-genus from the disclosed prior art genus and not "try the range of substituents." Second, the compounds are non-obvious over Ford-Hutchinson in view of the arguments made above. Third, one skilled in the art would in no way be motivated modify the compounds taught by Ford-Hutchinson to arrive at the presently claimed compounds and then be motivated to use them for Alzheimer's disease based on Watanbe in view of the structural differences discussed above.

Based on the foregoing, withdrawal of the obviousness rejection of Claims 5 to 7, 9 and 11 is respectfully requested.

Applicants submit the rejection of the compound and pharmaceutical composition claims have been overcome. Rejoinder of the process claims 12 and 13 pursuant to M.P.E.P. § 821.04 is respectfully requested.

Applicants respectfully submit that the application is in condition for allowance and passage thereto is earnestly requested. Any fees required in connection with this Reply may be taken from Merck Deposit Account No. 13-2755. The Examiner is invited to contact the undersigned attorney at the telephone number provided below if such would advance the prosecution of the case.

Respectfully submitted,

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